Clinical features in Adolescence among Genetically Confirmed Vascular Ehlers-Danlos Syndrome in Japanese: A Retrospective Study

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SCIENTIFIC MEETING - RARER TYPES
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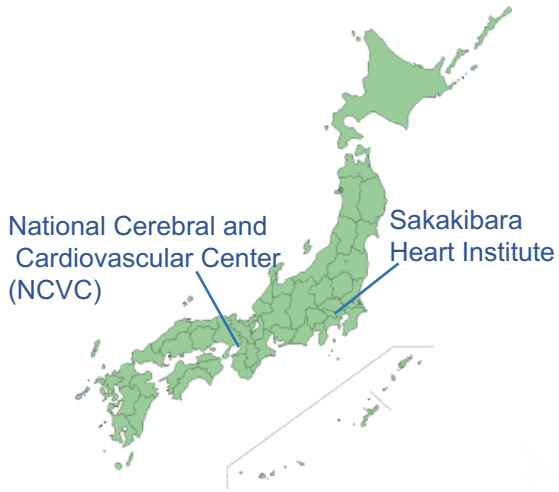
Disclosure of Conflict of Interest

Name of Speaker : Hiroko Morisaki

The author has no COI

to disclose with respect to this presentation

My experience managing CTD clinics in Japan



Connective Tissue Disorder(CTD) clinic
in cardiovascular specialty hospitals

2003-2016.3 NCVC (Osaka)
2016.4- Sakakibara Heart Institute(Tokyo)

Patients with vEDS are often misdiagnosed as Marfan syndrome or Loeys-Dietz syndrome when they are referred.

Vascular EDS: Clinical Characteristics (in literature)

- *Tissue fragility of arteries, intestine, uterus and ligaments*
  - *Arterial aneurysms, dissection, or rupture*
  - *Intestinal rupture*
  - *Uterine rupture during pregnancy*
- *Easy bruising*
- *Thin, translucent skin*
- *Others*
  - *Hypermobility of small joints, tendon/muscle rupture*
  - *Acrogeria*
  - *Early-onset varicose veins*
  - *Carotid-cavernous fistula (CCF)*
  - *Pneumothorax/pneumohemothorax,*
  - *Clubfoot, hip dislocation, limb deficiency*

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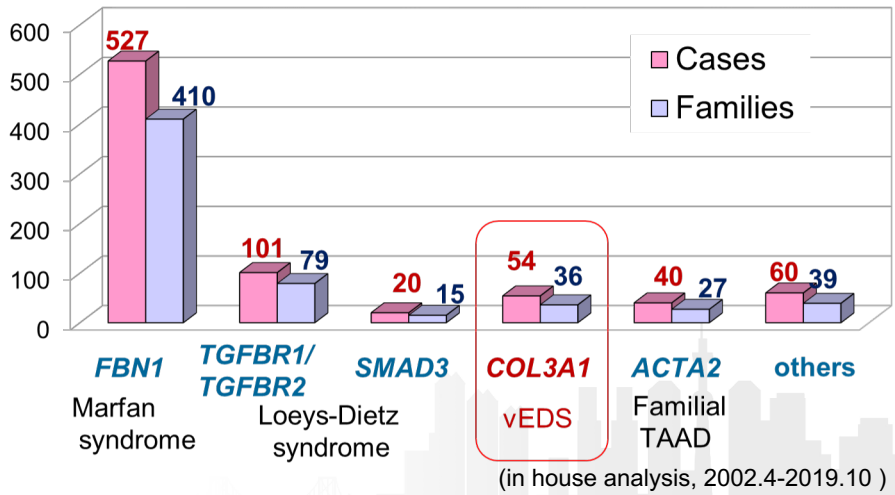
**Often observed in other hereditary TAAD (Thoracic Aortic Aneurysm & Dissection) syndrome, including MFS or LDS.*

Genetic Analysis of TAAD-related Genes in our Clinic



(in house analysis, 2002.4-2019.10)

Methods of Genetic Testing of Vascular EDS : COL3A1

(2002-2014)
RT-PCR sequencing (Sanger method) using mRNA from
- Dermal fibroblasts obtained from skin biopsy specimen
- Fibroblasts from surgically excised aortic tissues

(2015-2016.6)
Exonic DNA analysis (Sanger method +MLPA) using genomic DNA from
- Peripheral Lymphocytes

(2016.7- now)
Multigene Panel testing (NGS method)
- Marfan synd, Loeys-Dietz synd, vEDS, classical EDS, CHST14, FLNA, FTAAD, OI, etc

Natural History of vEDS (in literature)

- *25% of the vEDS have experienced a significant medical problem by age 20 years, 80% by age 40 years. (Pepin 2000)*
- *The majority of individuals were ascertained on the basis of a major complication (70%), at an average age of 30 years. (Pepin 2014)*
- *The median age of death was 51 years with a very large range. (Pepin 2014, Frank 2015, GeneReviews)*

Vascular EDS in Youth (in literature)

- *The majority (60%) of individuals with vEDS who are diagnosed before age 18 years are identified because of a positive family history (Pepin 2014).*
- *Without family history, the diagnosis of vEDS is rarely considered in childhood even with excessive bruising (Byers 2017)*
- *Approximately half of children tested for vEDS without family history present with a major complication at an average age of 11 years, … distal joint hypermobility, easy bruising, thin skin, and clubfeet – are most often present in those children ascertained without a major complication.*
- *Increased risk of sudden death from vascular rupture under age 20 in males (Pepin 2014)*

Aim of This Study

To describe clinical features in adolescence among Japanese vEDS patients

【Subjects】

54 molecularly diagnosed vEDS patients (36 families),

(excluding asymptomatic children (<11y))

【Characteristics of Interest】

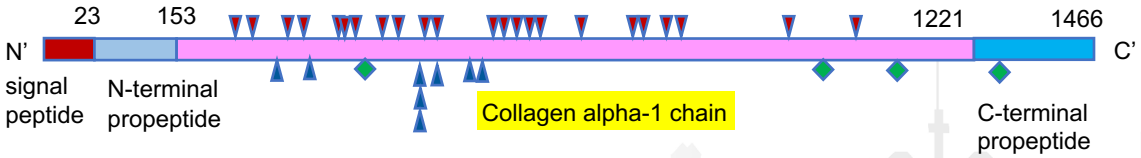
- molecular characteristics (variants)
- general characteristics (ex: sex, age of onset)
- perinatal complications
- clinical features in childhood
- major complications under age 20

(Clinical data collected from medical records/history taking during visit)

COL3A1 Mutations Found in 36 Index Cases

COL3A1 gene pathogenic variants

- 23 Gly substitution in triple helical domains (▼)
- 9 splice site mutation(▲)
- 4 PTC(premature termination codon) causing NMD(◆)

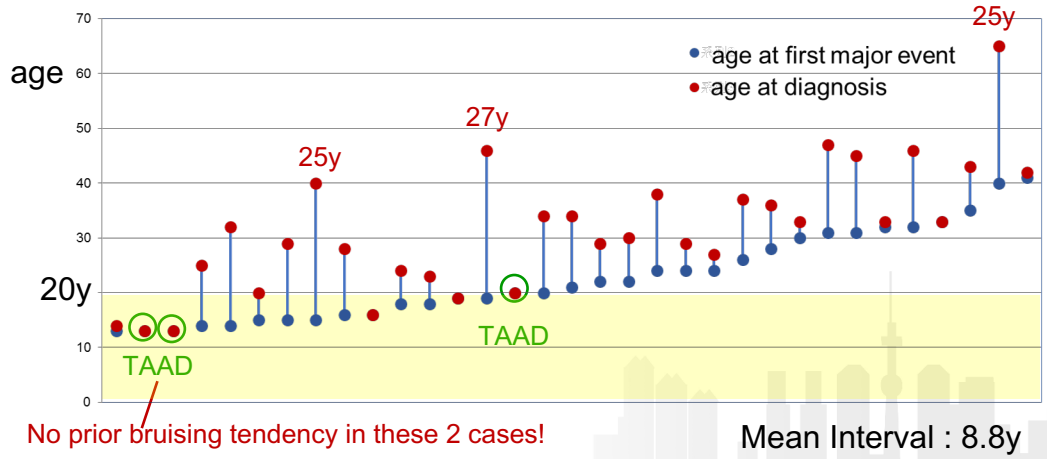


General Characteristics

		all	male	female
Number		54	25	29
	index cases	36	24	12
	relatives	18	1	17
mean age at diagnosis (y)		32.3	28.5	35
	index cases	30.6	29.3	33.1
	relatives	34.9	11	36.4
mutation type	Glycine	37	18	19
	Splicing	12	3	9
	Premature Termination	5	4	1
Mean age at first major complication*		22.5	22.8	22.1
# of Pts with first major complications under age 20		17(31.5%)	10(40.0%)	7(24.1%)

* Index cases only

Age at First Major Event and Diagnosis (Probands in the Cohort)



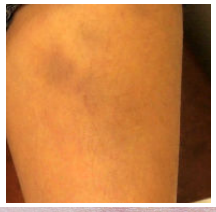
Mean Interval : 8.8y

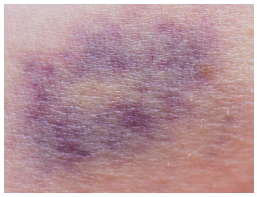
Perinatal Complications

- 5 premature ruptures of membrane (9.4%)
  @32-36W
- 3 clubfoot (5.7%)
- 2 cryptorchidism (2/25=8%)
- 1 bilateral hip dislocation
- 1 Inguinal hernia
- 5 congenital heart defects (9.4%)
  4 pulmonary valvular stenosis (PS)
  (3 balloon valvuloplasty)
  1 ventricular Septal Defect (VSD)
- 2 congenital pyloric stenosis (3.8%)

Bruising Tendency in Childhood

- Bruising tendency in childhood was observed in 38 of 54 pts.
  - 14 males (14/25=56%)
  - 24 females (24/29=83%)





Major complication*	Easy bruising in childhood	
	yes	no
yes	28	12
no	10	3

* Aortic dissection, arterial rupture, organ rupture (p=0.54)

Patients who showed no bruising tendency in childhood also experienced major vascular complications.

Major Vascular Complications in Adolescence

3 Aortic dissection(@ 13y, 13y, 20y, all males)

3 Intracranial hemorrhage
- subdural hematoma @ 15y (male)
- subarachnoid hemorrhage@19y (female)
- carotid-cavernous fistula @ 20y (female)

4 Rupture/dissection of middle sized arteries
- femoral artery @ 13y(male)
- celiac artery @ 14y (male)
- gastric artery @ 18y (female)
- coronary artery@19y (male)

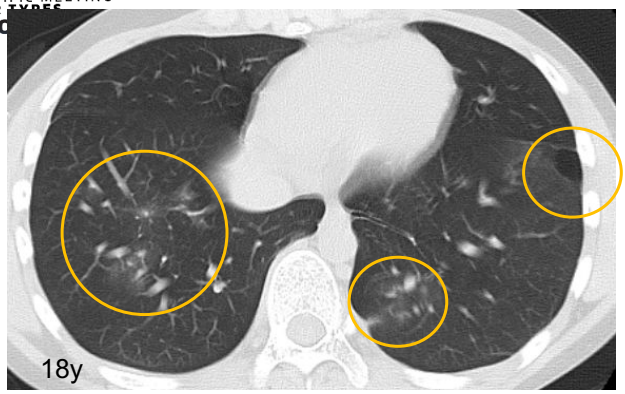
Non-vascular Complications in Adolescence

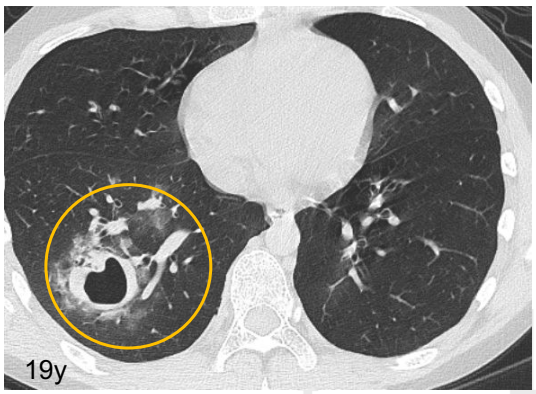
- 8 Pneumothorax/pneumohemothorax
- 4 Tendon/muscle rupture(severe injury)
  - Anterior cruciate ligament @ 16y female
  - Sternoclavicular joint @ 18y female
  - Rotator cuff at shoulder @17y male
  - Achilles tendon @ 15y female
- 3 Bowel ruptures @ 0y, 14y, 15y

Lung Complications in vEDS: (in the Literature)

- *Spontaneous pneumothorax is seen in 12% of individuals, often as a first manifestation.(Byers et al, 2017)*
- *The rare presentation of vascular EDS with pneumothorax, intrapulmonary hematomas, or hemothorax seems to occur often in young adults.(Abrahamsen et al, 2015)*
- *Fibrous pseudotumors and cyst formation in the lungs in EDS.(Corrin et al, 1990)*
- *Spontaneous laceration of lung tissue is an essential feature and followed by haematoma and possible fibrous nodule formation. (Kawabata et al, 2010)*

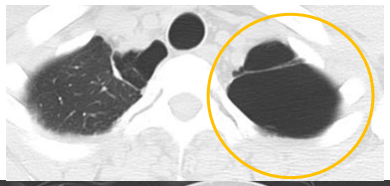
Lung CT images



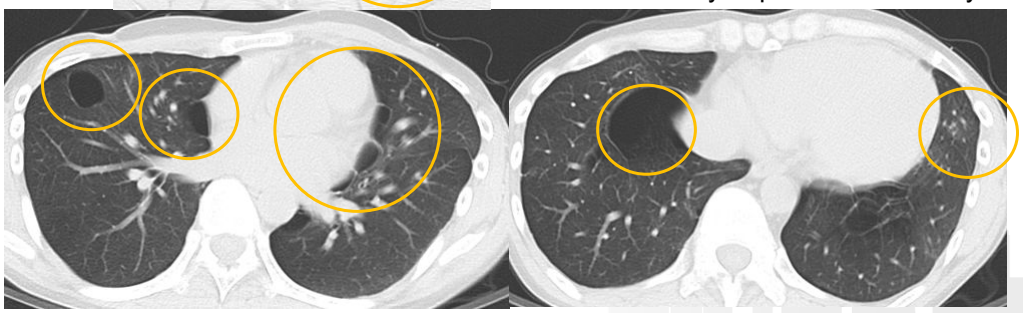


20y male
- 13y rupture of celiac artery
- 14y pneumothorax
- 18y pneumothorax/hemoptysis
- 19y coronary artery dissection

Lung CT images



32y male
- 14y pneumothorax
- 15y subdural hematoma
- 32y rupture of iliac artery



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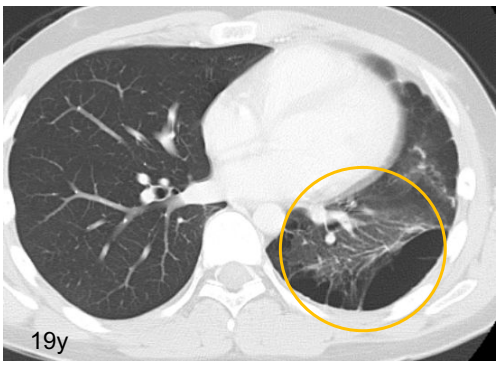
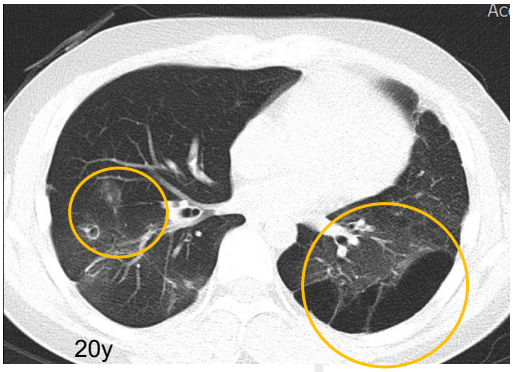
Lung CT images





21y male
- 18y Lt. pneumothorax/hemoptysis (2x)
- 19y Rt. pneumothorax/hemoptysis

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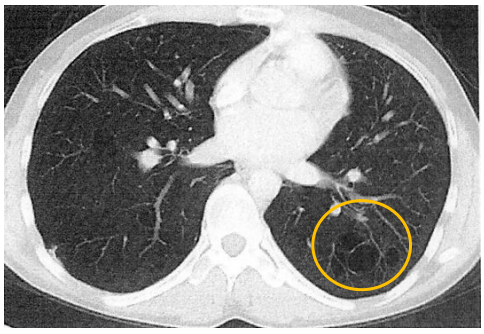
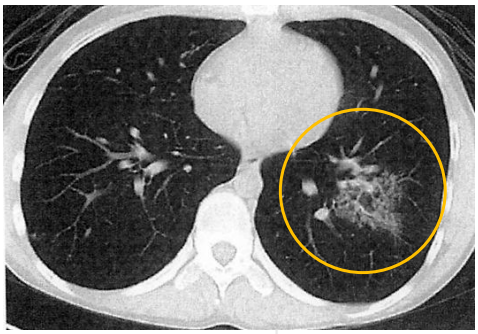
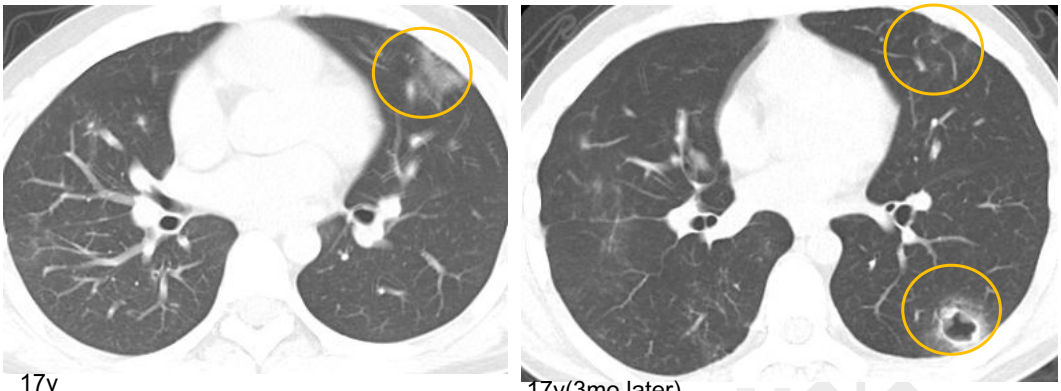




26y male
- 0y cryptorchidism, clubfoot
- 17y shoulder dislocation
- 19y recurrent pneumothorax
- 24y massive hemoptysis

Lung CT images



17y

17y(3mo later)

18y male
0y cryptorchidism, pyrolic stenosis
16y hemoptysis
17y massive hemoptysis

Lung Complications in vEDS in This Cohort

		Lung complications(≦20ys)		
		+	-	all
Vascular complications (all ages)	+	10 (7)	28 (31)	38
	-	2 (1)	13 (14)	15
	all	12 (8)	41 (45)	53

The proportion of patients who experienced lung complications under age 20 was much higher (18.4%) among those who experienced vascular complications, compared to those who did not (6.7%).

Summary of Patients Experiencing Lung Complications in Adolescence

- 87% (7/8) had massive hemoptysis
- 75% (6/8) had distinctive pulmonary CT images (multiple giant bullae or parenchymal hemorrhage (mostly in lower lobes))

- The majority (7/8=87%) of experienced major vascular complications sometime in their lives.
- For half (4/8=50%), pneumothorax or hemoptysis was the first significant event of tissue fragility.

Summary

- Recurrent pneumothorax accompanied with giant bullae and/or hemoptysis in adolescence is not a rare complication among vEDS patients in Japan.
- Such patients may have high risk of developing vascular complications later in life.
- Thus, for patients with such distinct symptoms, we recommend clinicians to suspect vEDS and consult geneticists for further testing.

Acknowledgement

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Thank you!